What is claimed is:

1. A method for mutagenesis comprising steps of:

a DNA synthesis in which one or more primers which have a nucleotide sequence containing at least one mutation and a phosphorylated 5'-terminus are annealed to a template DNA and then subjected to an elongation reaction using a thermostable high-fidelity DNA polymerase, after which the phosphorylated 5'-terminus and the elongated terminus are ligated by means of a thermostable DNA ligase to synthesize a circular DNA containing said primers;

a digestion in which said step of DNA synthesis is repeated several times to amplify the DNA containing said primers and, then, at least DNAs other than the amplified circular DNA are digested into several fragments; and

a double-stranded DNA synthesis in which, with the several fragments obtained in said step of digestion as megaprimers, said megaprimers are annealed to said circular DNA synthesized in said step of DNA synthesis, followed by an elongation reaction performed using said thermostable high-fidelity DNA polymerase.

2. The method for mutagenesis according to Claim 1 wherein, in said step of DNA synthesis, several of said primers are used to introduce mutations at multiple sites simultaneously.

3. The method for mutagenesis according to Claim 1 or 2 wherein, in said step of DNA synthesis, degenerative primers are used as said primers to introduce random mutations at certain sites in a nucleotide sequence.

4. The method for mutagenesis according to any one of Claims 1 to 3 wherein, during said step of double-stranded DNA synthesis, an auxiliary primer complementary to a region adjacent to the nucleotide sequence in which mutations are introduced, is added.

5. The method for mutagenesis according to Claim 4 wherein said auxiliary primer

is T7 primer.

6. The method for mutagenesis according to Claim 1 wherein, in said step of digestion, methylated and hemi- methylated nucleotide sequences are selectively cut.

7. The method for mutagenesis according to Claim 1 wherein, in said step of digestion, DpnI is used.

8. The method for mutagenesis according to Claim 1 wherein the thermostable high-fidelity DNA polymerase and/or thermostable DNA ligase used in said step of DNA synthesis are used in said step of double-stranded DNA synthesis.

9. The method for mutagenesis according to Claim 1 wherein, in said step of DNA synthesis, the entire step is completed in a reaction solution comprising at least said primers, said template DNA, said thermostable high-fidelity DNA polymerase and said thermostable DNA ligase.